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Kniest Dysplasia: Radiologic, Histopathological, and Scanning Electronmicroscopic Findings

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We describe severe neonatal Kniest dysplasia. Radiological findings in a severe case include short bowed tubular bones with exaggerated metaphyseal flare, moderate platyspondyly with vertical clefts of the vertebral bodies, and characteristically shaped iliac bones. Pathologic findings included a disorganized physeal growth plate, soft crumbly cartilage with a "Swiss-cheese" appearance, and diastase resistant intracytoplasmic inclusions in the resting chondrocytes. Transmission electronmicroscopy showed dilated cisternae of rough endoplasmic reticulum with finely granular material of accumulated protein. Scanning electronmicroscopy documented striking fragmentation and disintegration of collagen fibrils resulting in a web-like pattern and large open cyst-like spaces, and deficiency and disorganization of the collagen fibrils.

KEY WORDS: Kniest dysplasia, osteochondrodysplasia, radiology, pathology, transmission and scanning electronmicroscopy

INTRODUCTION

Kniest dysplasia, first described by Kniest in 1952, is a generalized disorder of connective tissue characterized by short-trunk dwarfism with kyphoscoliosis, prominent joints, midface hypoplasia, prominent eyes, cleft palate, hearing loss, myopia, and/or retinal detachment [Roaf et al., 1967; Larose and Gay, 1969; Silverman, 1969; Maroteaux and Spranger, 1973; Spranger and Maroteaux, 1974; Siggers et al., 1974; Brill et al., 1975; Kim et al., 1975; Lachman et al., 1975; Stanescu et al., 1977]. Pathological changes with soft crumbly cartilage and cottage cheese-like consistency have been described with microscopic changes of poorly staining cartilage with myxoid degeneration, PAS positive cytoplasmic inclusions corresponding to the transmission electronmicroscopic finding of dilated rough endoplasmic reticulum containing pools of proteinaceous material [Horton and Rimon, 1970; Gilbert et al., 1987; Rimoin et al., 1974, 1979; Rimoin, 1975].

Kniest dysplasia is an autosomal dominant condition. However, most cases represent new dominant mutations. The disorder has been observed in a parent and child in at least two cases [Spranger and Maroteaux, 1974; Kim et al., 1975]. Radiological findings were described by the authors listed above. Chen et al. [1980] described the changes in a 26-week-old fetus with Kniest dysplasia. Langer et al. [1976] and other investigators [Rolland et al., 1972; Dinno et al., 1976; Gruhn et al., 1978] have observed similar radiological changes in dyssegmental dwarfism (Rolland-Langer-Dinno syndrome) in which familial occurrence suggests autosomal recessive inheritance. Pathological findings have included disorganization of the growth plate, deficiency of collagen matrix, and proteinaceous inclusions in the resting chondrocytes demonstrated also by transmission electronmicroscopy [Rimoin et al., 1974; Siggers et al., 1974; Silberberg, 1974; Stanescu and Maroteaux, 1975; Chen et al., 1980; Gilbert et al., 1987]. Scanning electronmicroscopy has not been described previously.

Clinical Data (Case 1)

D.K. was born at 38 weeks gestation to a 29-year-old gravida 2, para 1 mother. She reported "flu-like" symptoms at 3 weeks but had no other known exposure to potentially hazardous agents. Fetal movements felt less active than during her previous pregnancy 3½ years earlier which had resulted in a healthy girl.

Delivery of the propositus was breech, his birth weight and length were 3,300 g and 41 cm, respectively, head circumference (OFC) was 36.25 cm, and Apgar

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

scores were 7 and 8 at 1 and 5 minutes, respectively; he was immediately noted to have short limbs and he required suctioning, oxygen, and had cyanotic episodes, retractions, and feeding difficulties postnatally and after discharge home at age 6 days.

The infant was hospitalized at age 11 weeks for evaluation of cyanotic spells, which were attributed to tracheomalacia. At that time he was found to have profound hearing loss, poor but present visual responses with high myopia, and possible cupping of optic nerves. His equinovarous feet were casted and an underlying diagnosis of Kniest dysplasia was suspected.

The infant was discharged to a residential institution because his parents could neither cope with his dwarfism nor the multiple needs associated with it.

At age 11 months he was hospitalized and his condition had improved quite considerably. His length and weight were 56 cm (mean for 2 months) and 8,200 g (3rd centile), respectively, OFC was 47.3 (75th centile).

On physical examination (Fig. 1), his head was brachycephalic, asymmetric with right occipital flattening and fine blond hair; the anterior fontanelle was 6 × 3 cm. The face was round, flat, and asymmetric with hypoplastic lateral zygomatic arches, large prominent eyes with shallow orbital ridges, light blue sclerae, and irides with pupils reacting poorly to light. He had a flat nasal bridge, short upturned nose, long philtrum, and downturned mouth. Ears appeared normally differentiated; tympanic membranes were visible. His mouth was large, with downturned corners, tongue with tight frenulum, short cleft palate, and 2 upper and 2 lower middle incisors; gag was present and suck was strong. The neck was short, the chest appeared small, and no murmur was heard. The abdomen was protuberant, liver firm and down 3 cm, and the spleen was also down 2–3 cm. There were no hernias. Genitalia were normal and testes descended. The back was straight, with a short spine. The hips had limited ROM, could not abduct, and rotation was limited. Knees, elbows, shoulders, and large joints all had limited ROM. The infant had very short humeri and femora, distally with less shortness, while hand and foot size approached normal: they appeared broad, moved well, and with good grasp; feet had metatarsus adductus and hindfoot varus.

Neurologically he was alert and appropriately afraid of the examiner, but able to be comforted. He looked around and fixed well: response to visual and touch stimuli was normal. He moved his limbs in a limited way quite vigorously and rolled over from front to back and back to front easily by himself. He had poor head control and could not sit. Muscle tone was difficult to evaluate because of lack of ROM at joints. He had no speech.

Psychologically, he was interactive and responsive to people; he seemed alert, appealing, and appropriate for a deaf child without auditory stimuli.

Evaluations included a skeletal survey which showed maturational changes and generalized osteoporosis consistent with Kniest dysplasia. A costochondral junction bone biopsy, done during myringotomy, demonstrated grossly dysplastic crumbling cartilage and bone. A brain CT scan showed calvarial asymmetry, fluid collections in the Sylvian cisterns and middle cranial fossa, with moderately enlarged lateral ventricles; EEG was normal.

At age 3$\frac{4}{12}$ years, he underwent general anesthesia prior to surgery for bilateral heel cord lengthening and developed malignant hyperthermia. It was possible to treat effectively and prevent any unfavorable consequences of this unexpected reaction and the surgical procedure, which also included bilateral triple arthrodeses for correction of equinovarus clubfeet, was performed successfully 1 week later.

His development at chronological 10½ months, as assessed on the Bayley Scales of Infant Development, eliminating those items requiring hearing, was consistently at or above the 6–7 month level. He moved by scooting on the floor on his bottom and around age 3

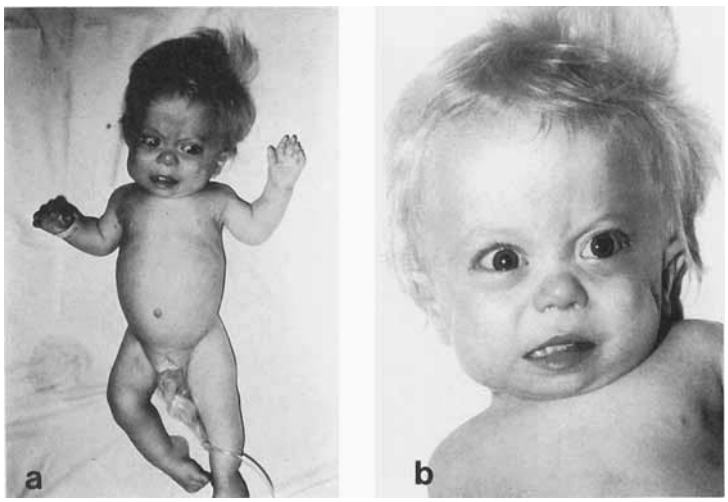

Fig. 1. (Case 1) Infant with Kniest dysplasia with large head, flat face, short neck, short trunk, protruberant abdomen, and moderately short limbs with prominent joints. **a:** Full body view. **b:** Face.

years, he began to stand and cruise around furniture with difficulty. At the time of his hospitalization for heel cord lengthening at age 3 9/12 years, the physicians and therapists caring for him recognized that his potential for physical, social, and intellectual development was far greater than previously anticipated. Placement in foster care or adoption, as opposed to permanent placement in the residential institution, was suggested and the child was subsequently adopted at age 5 years.

The patient was evaluated most recently at age 17 years. He had normal intelligence, profound deafness (primarily sensorineural), and communicated by signing.

His visual defect which had been characterized by high myopia, vitreoretinal dystrophy, and cataract formation, had deteriorated progressively. At 10½ months he had −11.5 diopters OD and −12.5 diopters OS; at 5 years he had −15 diopters OD and −16 diopters OS. At age 10 years he had cataract surgery in the right eye and developed a large retinal tear. This reattached after 2 months and he had 20/200 vision with $+2.5 \times (-17.5) \times 14$ at age 17. The left eye was developing a cataract and it was operated with prophylactic retinal reattachment surgery. His vision was 20/60 with −17.5 diopter lens. Subsequently he has also had a corneal transplant in the right eye.

Contractures at hips, knees, ankles, elbows, wrists, and hand joints were associated with increasing pain in these joints and also in the temporomandibular joints. He had little ankle motion and a fixed planovalgus deformity of the hindfeet. He underwent osteotomies of both femora and tibiae and fusion of the left knee joint. He also had marked lumbar hyperlordosis. At age 17 years he had markedly reduced activity and there had been progression of a thoracic kyphoscoliosis; preoperative evaluation showed restrictive lung disease due to the deformity from the kyphosis. He also had reactive airway disease with compression of the trachea because of a narrow bony thoracic inlet which necessitated a tracheostomy preoperatively. During the operation the kyphotic curve was fused at 90°. His height at that time was 125.6 cm. Limitation of joint motion and joint pain continues.

Pathological Findings (Figs. 2–5)

A biopsy of cartilage was taken from the physis of the talus. The resting, proliferative, and lytic zones of the cartilage were all abnormal and showed honeycomb-like cystic changes which appeared to be more striking at the physeal plate. Capillary infiltration also appeared to be diminished and special stains using Alcian blue demonstrated pools of glycosaminoglycan in some of the cystic areas. The appearance was that described as "Swiss cheese." The resting cartilage contained PAS-positive inclusions. The cartilage matrix was deficient with marked variability of staining intensity. Echondral bone formation was sufficient and little osteoid appeared to be formed. There were very small areas of ossification at the growth plate.

Transmission Electronmicroscopy

A portion of the tissue was placed in 2.5% glutaraldehyde, post-fixed in osmium tetroxide, and embedded in epon. Ultrathin sections were cut on an ultramicrotome and examined in a Hitachi-9 electronmicroscope. There was vacuolar degeneration of the extralacunar matrix. The cartilage fibrils were sparsely distributed and fine. Dilated rough endoplasmic reticulum was filled with finely granular proteinaceous material.

Scanning Electronmicroscopy

The most striking characteristic was the disintegration of the cartilage fibrils resulting in a web-like fine fibrillar appearance in some areas with large open cyst-like spaces irregularly distributed throughout the cartilage. In some areas collagen fibrils aggregated into thicker bundles enveloped by thin circular strands although for the most part they were sparsely distributed.

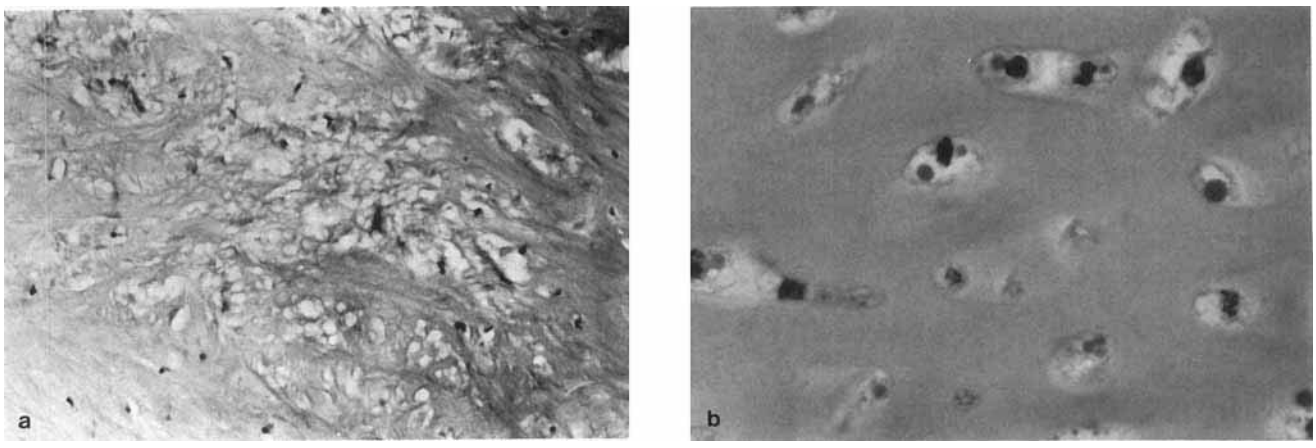

Fig. 2. (Case 1) **a:** Microscopic section from resting cartilage showing chondrocytes separated by myxoid cartilaginous matrix. H&E, ×100. **b:** High-power view of resting cartilage showing inclusions in cytoplasm of the chondrocytes. ×400.

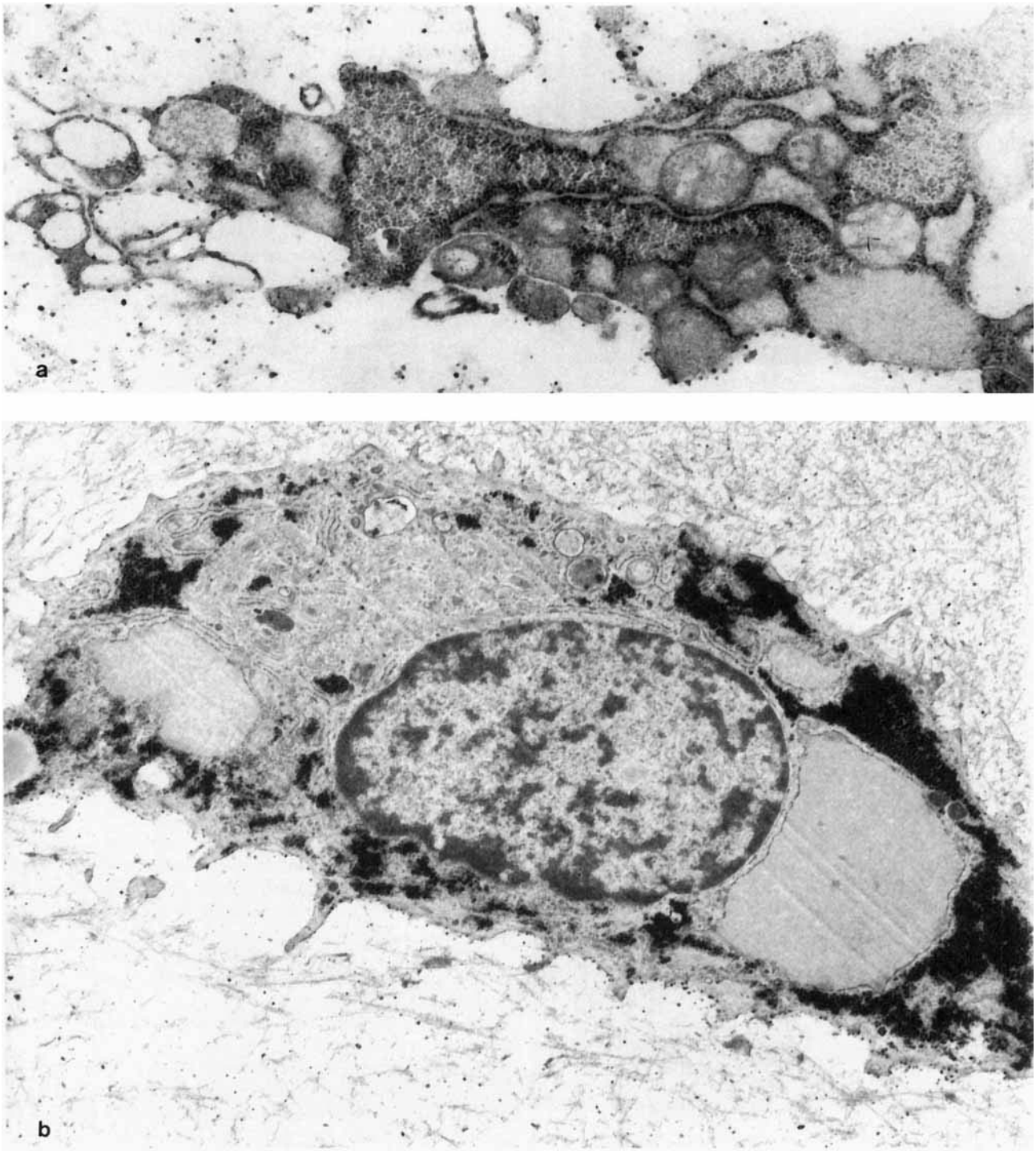

Fig. 3. **a:** (Case 1) Electronmicrograph showing chondrocytes with dilated rough endoplasmic reticulum filled with finely granular deposits. (×8,780). **b:** High power view (×12,390).

Clinical Summary (Case 2) (Fig. 6)

B.M. was born to a 27-year-old gravida 7, para 3, Sp-ab 4, mother and a 26-year-old father. The two older healthy maternal half sibs each had different fathers, as did the miscarriages. No one in either family was known to have had a disorder similar to that in the propositus, although one female paternal cousin was reported to have had a cleft palate. The pregnancy was uncomplicated and apart from smoking one pack of cigarettes per day and a documented episode of febrile "flu" (treated with Tylenol®3, Datril®, and Codeine) in the 2nd trimester, exposure to potentially hazardous

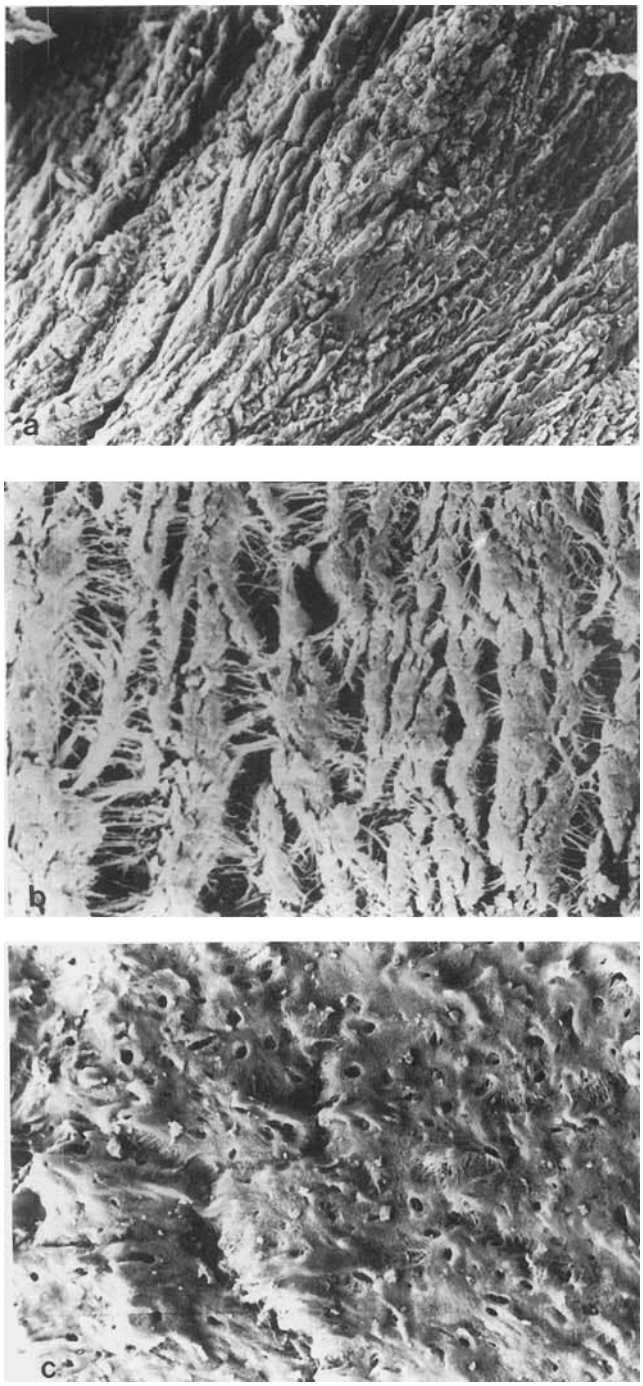

Fig. 4. **a:** (Case 1) Scanning electronmicroscopy. Relatively normal appearing cartilage showing fibrils aggregated into closely applied bundles. ×400. **b:** Higher magnification with lattice-like fibrils separating the thicker bundles of collagenous fibrils. ×2,000. **c:** Cross section of surface of cartilage showing fine webs of fibrils between cells. ×200.

agents was denied. Delivery was vertex and pitocin-induced at term by reliable dates. Birth weight was 2,500 g, length was 41 cm, and OFC was not recorded, but head noted as "large," Apgar scores 8 and 9 at 1 and 5 minutes, respectively. The umbilical cord had three vessels, placenta appeared normal, and there were no perinatal complications. He had a midline cleft palate, mandibular microretrognathia (Fig. 6a), and short, abnormal lower limbs and feet (Fig. 6b). A diagnosis of Pierre-Robin sequence with rhizomelic lower limb shortness was suggested characterized by radiological metaphyseal dysplasia, joint enlargement, and minimal joint contractures. He was unable to nurse and a gastrostomy was placed shortly after birth.

Additional early evaluations included a brainstem evoked response at age 3½ months which was consistent with bilateral severe to profound hearing loss and a brain CT scan which showed asymmetry of the cranial vault with prominence of the Sylvian suture without other abnormalities.

The patient was first seen in genetics clinic at age 5 months and during his two subsequent hospitalizations. He was a brown haired, brown eyed infant with plagiocephalic, asymmetric skull (with depression on the right and curvature on the left). He had bilateral wandering nystagmus, cleft palate, and obvious asymmetric (left shorter than right) rhizomelic limb shortness more severe on the lower than on the upper limbs.

More detailed physical examination showed narrow ear canals, with difficulty to visualize tympanic membranes, right torticollis, pectus carinatum, a grade I/VI systolic murmur, the liver 1–2 cm below the costal margin, and gastrostomy in situ. Examination of the limbs showed, in addition to the characteristics mentioned above, limited hip rotation with partial flexion contractures and bilateral foot eversion. The remainder of the physical findings were normal.

Neurological examination showed only fair head control, with good tone in ventral suspension. The patient was able to raise himself up on his arms in the prone position. The responses to touch and pain were appropriate. The pupils were equal and reactive to light, and other cranial nerves appeared to be intact. Although the neurologic examination was compatible with developmental delay, there were no focal motor or sensory findings which might have indicated spinal cord compression.

Abnormal laboratory findings included marked right ventricular hypertrophy on ECG, with an axis of −150°, a short PR interval, and deep Q waves in leads 2, 3, and AVF. An echocardiogram showed a prominent pulmonary artery but no clear evidence of cor pulmonale. Renal ultrasound study showed bilateral hydronephrosis and large ureters probably secondary to congenital webs or aberrant vessels causing obstruction at the uretero-vesicular junction. He also had an asymptomatic calcification in the lower pole of his right kidney.

A detailed radiographic skeletal survey was suggestive of Kniest dysplasia or a variant. It showed shortness of the long tubular bones with bulbous epiphyses, multiple anomalous vertebrae within the lumbar spine and sacrum, and clubfeet.

A biopsy of the right iliac crest of the physes showed a growth plate that was very sparse and uneven, but there were a few areas of disorganized chondrocyte proliferation and differentiation. The cartilage bone interface was irregular but the cartilage and bone matrices

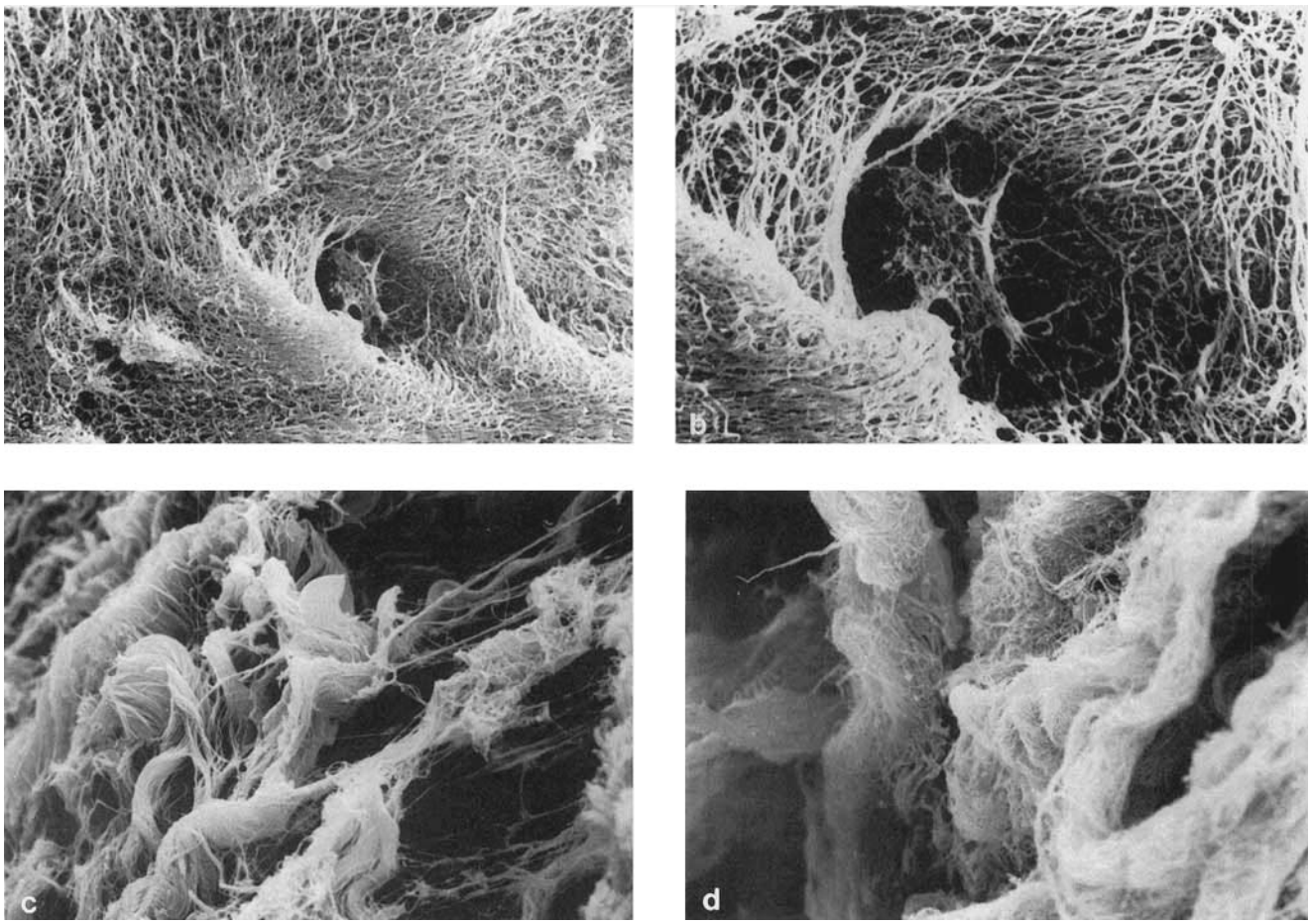

Fig. 5. (Case 1) Scanning electronmicroscopy. **a:** Section of cartilage: a honey-comb pattern with central area of cyst formation. ×1,800. **b:** Higher magnification of central cyst containing web-like wisps of collagen fibrils. ×4,400. **c:** Section of cartilage showing thick bundles of collagen with a swirled pattern enveloped by thin circular strands. ×2,000. **d:** Similar appearance to a with webbed pattern of tangled collagen fibrils with gaps between the collagen bundles. ×2,000.

appeared to be normally mineralized. The resting chondrocytes were irregularly dispersed and small areas of poorly stained fibrous appearing matrix were scattered throughout the resting cartilage. These stained strongly with alcian blue and were quite typical of Kniest syndrome.

The clinical course in this infant was one of progressive deterioration. He was rehospitalized at 12 months for upper airway obstruction, congestive heart failure, failure to thrive (weight at 12 months was 3,920 g), and mild renal insufficiency. Tracheostomy resulted in marked improvement and he was discharged at 14 months weighing 4,700 g.

Gross motor development was delayed. At 14 months he responded to light touch and visual stimulation (vision was thought to be intact), loud auditory stimulation and pain. He had poor head control, normal muscle tone, and social smile and was able to reach for objects. He vocalized little but it was possible to engage him.

He was admitted to a medical residential facility at age 14½ months and died 6 weeks later of respiratory failure. No autopsy was performed.

Clinical Findings (Case 3)

This 2-month-old black girl was born at 30 weeks of gestation by cesarean section to a 35-year-old G6 P5 A1 mother. Premature rupture of membranes occurred 24 hours before delivery. The patient had poor oxygenation, was intubated, and placed on intermittent ventilation. Roentgenograms of the chest showed cardiomegaly and small thoracic compartment. The day after delivery she was alert, tachypneic, and had clear breath sounds, a systolic ejection murmur, short limbs, bowing of legs, decreased humerus to ulna ratio, clinodactyly of the fifth digit, and a small thoracic cage. An echocardiogram showed a large PDA with right to left shunt thought to be secondary to pulmonary hypertension. The echocardiogram also showed normal anatomy of the heart with severe mitral regurgitation, large left atrium, and mild tricuspid regurgitation. Blood cultures grew group B streptoccus; penicillin was administered.

A skeletal survey showed wide interpedicular distance of the spine, short ribs, and delay in sternal ossi-

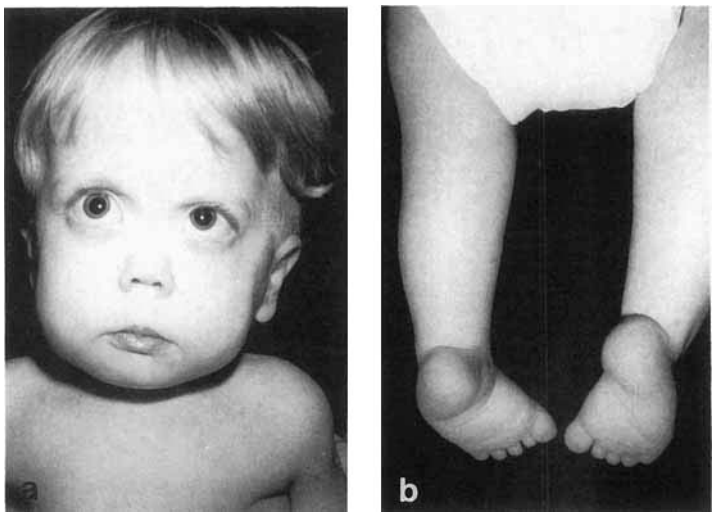

Fig. 6. (Case 2) Infant with Kniest dysplasia. **a:** Large head, flat face, anteverted nostrils and prominent eyes. **b:** Abnormal feet with protrusion and prominence of calcaneus and varus deformity.

fication; the humeri and femora were short and thick with wide metaphyses. The pubic bones were thick and short. Asphyxiating thoracic dystrophy was suspected. She continued to have heart failure with tachypnea.

At 1 month of life, the patient was reintubated because of labored breathing with left lower lobe atelectasis with increased heart rate and cardiomegaly. Respiratory difficulty continued, bradycardia ensued, and finally cardiac arrest. The patient died at age 5 weeks.

Pathological Findings (Fig. 7)

Pertinent autopsy findings included small thoracic cage with normal lung development, short ribs with prominent costochondral junction, delayed sternal calcification, short upper and lower limbs (short tubular bones with broad proximal and distal ends), bowed legs (femur and tibia), small pelvis with thick ischia (by roentgenography), platyspondyly (by roentgenography), and normal head OFC with increased A-P diameter (dolichocephaly).

Microscopic examination of sections of rib and clavicle showed lakes of Alican blue positive mucoid material (Swiss-cheese type degeneration) in the resting cartilage. The proliferative zone was irregular without orderly arrangement; a few mucoid lakes were also present. The hypertrophic zone was broad and the chondrocytes were not aligned in parallel columns. The zone of provisional calcification was disorganized and invaded irregularly by capillaries. A few vessels penetrated the proliferative zone, and at times the resting cartilage zone. PAS positive finely granular inclusions were present in the resting cartilage. Transmission electronmicroscopy showed dilated rough endoplasmic material containing proteinaceous material and fine collagen fibrils.

Radiological Findings in the Newborn Infant With Kniest Dysplasia (Figs. 8, 9)

The combination of the appearance of the pelvis, vertebrae, and long tubular bones is usually diagnostic or highly suggestive of Kniest dysplasia neonatally. The long tubular limb bones are short with broad metaphyseal flare. This appearance is often accentuated by foreshortening, especially of the femora. The foreshortening also makes the metaphyseal margins looks abnormally convex. There may be bowing, which is usually lateral, of the femoral and upper tibial shafts. The tubular bones of the hands and feet are either slightly short and broad or normal. There is usually no ossification of the epiphyses at the knees.

The basilar portion of the ilia is usually shorter than normal in relation to the iliac wings and is narrower than in many other short-limb conditions. Frequently, there is a downward directed bony spur at the lateral junction of the basilar portion and the iliac wing. Both tilting and turning of the pelvis can change the apparent shape of the ilia and lead to confusion with other neonatal short-limb bone dysplasias. The ischia are short and broad. The pubic bones are usually less well ossified than normal and may not be ossified.

The vertebral bodies are flatter than normal and have essentially parallel endplates rather than the convex endplates that are normal in the neonate. Ossification defects in the vertebral bodies are common. There may be narrow or broad coronal clefts through the body or there may be decreased ossification or absence of ossification of the posterior part of the body. These larger ossification defects most often involve the mid or lower thoracic bodies and the lower lumbar bodies. Differences in the size of adjacent bodies (anisospondyly) may be present. The lower lumbar bodies are often taller anteriorly than posteriorly (pear-shaped bodies). The bodies in the thoracolumbar junction region are often anteriorly wedged.

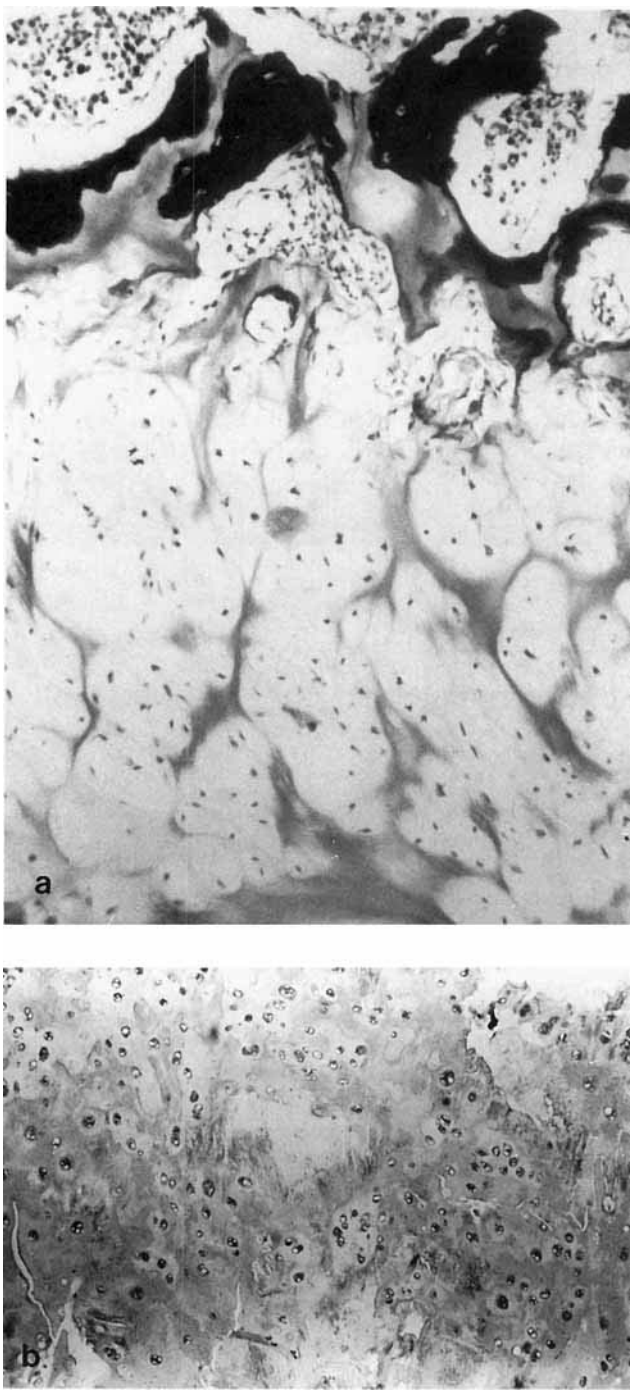

Fig. 7. (Case 3) **a:** Microscopic section showing disorganized growth plate and diminished capillary infiltration. Alcian Blue PAS. ×250. **b:** Microscopic section showing cystic spaces filled with Alcian Blue positive material within the resting cartilage. Note myxoid degeneration of the chondroid matrix. Alcian Blue. ×250.

Other radiological findings include a normal skull and clavicles and slightly short ribs.

Radiological Nosology

The combination of findings previously described in the pelvis, vertebral bodies, and tubular bones usually differentiates neonatal Kniest dysplasia (KD) from other neonatal short-limb bone dysplasias. However, changes in the position of the pelvis, especially tilting anteriorly or posteriorly, can change the apparent shape of the ilia. This can cause confusion with spondyloepiphyseal dysplasia congenita (SEDC) [Spranger et al., 1974] and the Weissenbacher-Zweymüller syndrome (WZS) [Giedion et al., 1982; Taybi and Lachman, 1990] which we think usually represents neonatal manifestation of a type of Stickler syndrome [Kelley et al., 1982] and of the Insley-Astley dysplasia [Insley and Astley, 1974]. KD can also be confused with mild cases of the less severe Desbuquois-Rolland type of dyssegmental dysplasia [Langer et al., 1976].

Despite the fact that the neonatal manifestations of SEDC differ considerably from those of KD, they have been confused. In SEDC the inferior margin of the ilium is almost as wide as the widest part of the iliac wing; it is slightly convex inferiorly, and the acetabular angle is small. The pubic bones are either underossified or unossified, and there may be a downward directed bony spur at the junction of the short basilar portion and the iliac wing as in KD. Some or all of the lumbar vertebral bodies have a pear shape, being taller anteriorly than posteriorly. The lower lumbar and the cervical bodies are the least well ossified. The limb bones are short with some broadening of the metaphyseal regions. Foreshortening from flexion contractures is rare.

In WZS the shape of the pelvis is similar to that of SEDC in that the basilar portions are relatively broad in relation to the iliac wings. The inferior margin of the ilium is more horizontal than it is in KD. The pubic and ischial bones are normally ossified. The lumbar bodies have essentially straight endplates or indentations at their midpoint. Often a narrow coronal cleft is present in this location. The limb bones are basically the same as in KD, but are less often foreshortened.

The mild form of dyssegmental dysplasia (Desbuquois-Rolland type) [Langer et al., 1976] has ilia similarly shaped to those of KD. The basilar portion is narrow compared to the iliac wings but is also short with a small sacrosciatic notch giving a somewhat different pelvic appearance from that seen in KD. The pubic and ischial bones are normally ossified in DD, while this is rare in KD. Most of the vertebral bodies are platyspondylic and coronal clefts, often broad, are common. Interspersed with these flattened coronally cleft bodies are large bodies that are usually anteriorly wedged and are tallest at the level of coronal clefts in the adjacent bodies. The limb bones which are short with exaggerated metaphyseal flare are often bowed. Posterior bowing is common in the femora, and the lower fibular shaft is often bowed.

Pathological Studies in Neonatal Kniest Dysplasia

Pathological and histochemical studies of the growth plate were described by Horton and Rimoin [1970]. Extensive vacuolar changes are observed throughout the endochondral growth plate and adjacent resting cartilage. These changes occur within the cartilage matrix and also in the lacunae of degenerating chondrocytes. The septa of the lesions contain chondroitin sulfate, but

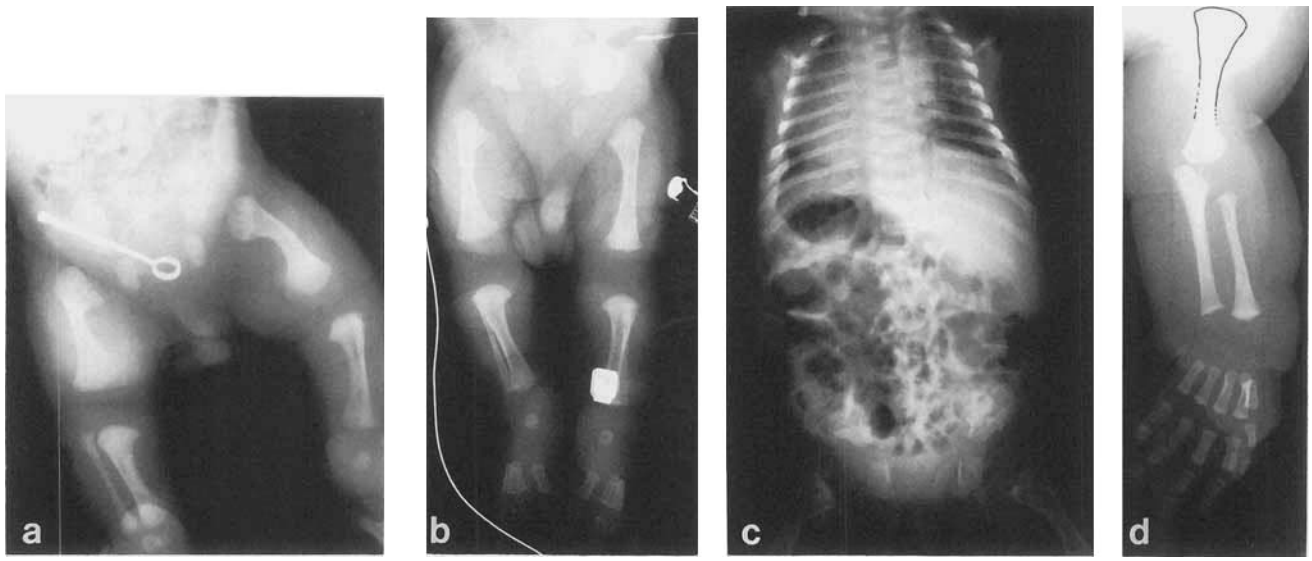

Fig. 8. (Case 1) Radiological findings in newborn infants with Kniest dysplasia. **a:** Severely affected newborn child. The basilar portions of the ilia are not significantly shortened. There is a normal relationship between the narrow basilar part and the flared iliac wings. There is ossification of pubic bones. The tubular bones are short with broad metaphyses and metaphyseal margins that appear convex. These changes are accentuated by foreshortening. The apparent difference is the shape of the proximal femora is largely due to positional differences. Lateral bowing of the left femur and upper tibiae is present. There is no epiphyseal ossification at the knees. **b:** Less severely affected newborn infant. Typical narrow basilar portions. No pubic ossification is present. Note difference in appearance of the two proximal femoral metaphyseal margins due to slight rotational differences. There is very little foreshortening of the bones. There is no epiphyseal ossification at the knees. **c:** Another newborn infant. Short ribs with the anterior ends immediately adjacent to the lateral-most part of the ribs. Platyspondyly in the thoracic vertebral bodies. The pelvis is typical. The heart and stomach are on the right. The femora are short with broad metaphyses. **d:** Another newborn infant. The humerus, radius, and ulna are short with slight increased flaring of the metaphyses. The tubular bones of the hands are normal.

little keratan sulfate or collagen. Resting cartilage not adjacent to the growth plate stains irregularly and shows few of the vacuolar lesions, and chondrocytes are enlarged and contain cytoplasmic inclusions, but no vacuolar material. Thus, there appears to be a sequence of events initiated by cellular accumulation of a substance that progresses to cellular and matrix degeneration.

A characteristic histopathologic picture of "Swiss cheese" cartilage with the numerous empty spaces lying within the resting cartilage is a consistent finding. Ultrastructural studies have shown that dilated cisternae of rough endoplasmic reticulum of the resting chondrocytes are filled with proteinaceous material and irregular aggregates of collagen are present in the resting cartilage matrix [Gilbert et al., 1987; Rimoin et al., 1974; Siggers et al., 1974; Silberberg, 1974; Stanescu and Maroteaux, 1975]. The septa stain with Alcian blue at 0.4 M $MgCl_2$, but staining is lost when the concentration is raised to 0.9 M and after hyaluronidase digestion, suggesting that the GAG is predominantly chondroitin sulfate rather than keratan sulfate [Horton and Rimoin, 1970]. Chondrocytes within the growth plate form slightly irregular columns. The matrix septa are wider than normal and often filled with proteinaceous material. The calcification of the cartilage septa at the chondro-osseous junction (provisional calcification) as well as the calcification of bone matrix appear to be normal.

The resting chondrocytes are larger than normal, irregularly shaped, and contain cytoplasmic inclusions which are PAS-positive not digested by diastase. A defect in the structure, synthesis, or secretion of a matrix component leads to its accumulation within the rough endoplasmic reticulum. It has been suggested that this may result in cell toxicity and premature degeneration of the chondrocytes. Because of this, the sequence of events initiated by the cellular accumulation of material within the chondrocytes may progress to degeneration of both cells and matrix.

Scanning electronmicroscopy in our studies have shown striking changes in the appearance and organization of collagen fibrils with disintegration of collagen resulting in vacuolar spaces and a lack of normal aggregation of collagen fibrils resulting in a fine web-like arrangement of collagen.

DISCUSSION

Salient manifestations in infants and young children with KD include the following: rhizomelic shortness more severe in the lower limbs, asymmetry of the skull (with disproportionately larger head circumference in comparison to decreased body length) characteristic facial appearance with midfacial hypoplasia, shallow supraorbital ridges, prominent eyes, cleft palate and downturned mouth, recognizable at birth and on prenatal ultrasound study.

Early postnatal tracheomalacia resulting in respiratory insufficiency and feeding difficulties with secondary failure to thrive are frequently potentially life

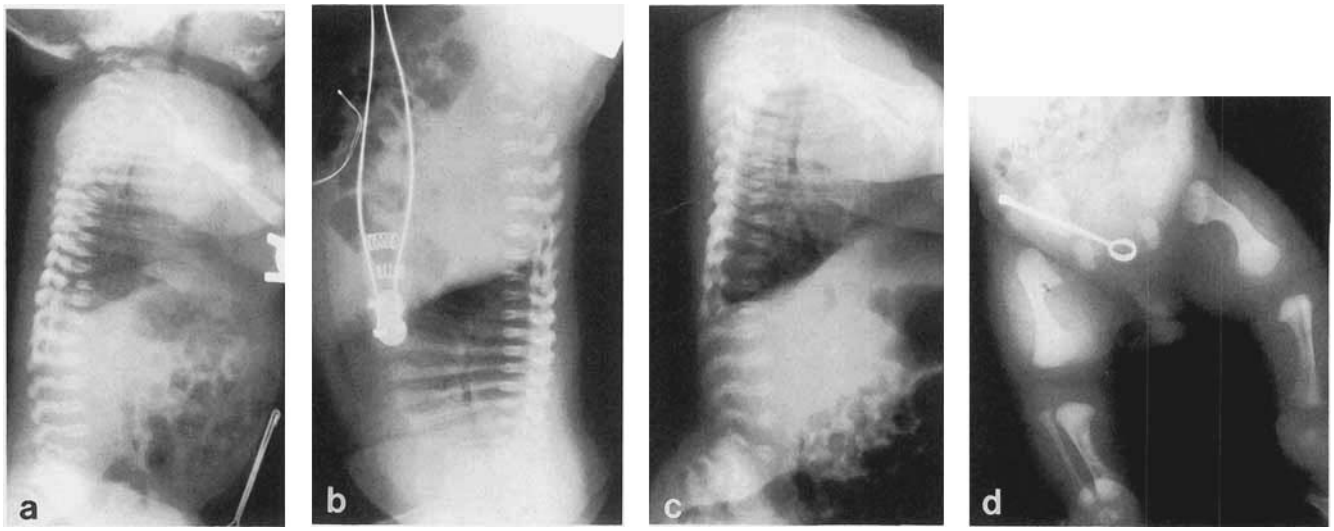

Fig. 9. **a:** (Same patient as Fig. 8a) Platyspondyly without the normal newborn endplate convexity of the vertebral bodies. Anterior wedging of the mid and lower thoracic bodies and L1. Absence of ossification in the posterior part of the body of T9. Decreased ossification of posterior aspect of body of L5. Note increased lumbosacral angle and slightly short ribs with cupped anterior ends in all patients. **b:** (Same patient as Fig. 8b) Platyspondyly with straighter than normal endplates. Narrow coronal clefts L1-4. Absence of ossification in posterior part of pear-shaped body of L5. **c:** (Same patient as Fig. 8c) Platyspondyly with straighter than normal endplates. The body of L2 is large compared with the other lumbar bodies (anisospondyly). Deficient ossification in the posterior parts of the bodies of L4 and 5. Pear-shaped lower lumbar bodies. **d:** Another newborn infant. Platyspondyly with straighter than normal endplates. Anterior wedged bodies in the thoracolumbar junction region. Absent or decreased ossification in posterior aspects of the bodies of T11 and L1,3,5.

threatening complications. Severe orthopedic disability is probably not avoidable in patients with KD, but careful, consistent management and follow-up by physicians acquainted with the whole patient and all implications of their disorder may ameliorate some of the devastating complications.

The true intellectual potential of children with KD is not known, and although their abilities are frequently masked by their multiple handicaps, it is probably that their intellect is unimpaired. Therefore it is essential that the characteristically profound hearing loss and any degree of vision impairment be detected as early as possibly so that specific, therapy can aid the child in reaching his/her maximum potential.

KD is one of the type II collagenopathies that range in clinical severity from lethal achondrogenesis type II (Langer-Saldino) and hypochondrogenesis through spondyloepiphyseal dysplasia, spondylometaphyseal dysplasia, KD, dyssegmental dysplasia to the Stickler syndrome, and familial precocious osteoarthropathy at the mildest end of the spectrum [Spranger et al., 1994; Mortier et al., 1995]. Periodic acid Schiff positive inclusions may be seen in the dilated rough endoplasmic reticulum in these cases in the resting chondrocytes, which has been shown in KD to be type II procollagen [Rogaret et al., 1994].

Protein analysis of collagen from the cartilage has indicated post translational over modification of the major cyanogen bromide peptides that suggests a mutation near the carboxyl terminus of the type II collagen molecule. Studies of the DNA have demonstrated that the phenotype is produced by a single base change (G→C) that results in the substitution of glycine^{691} by arginine in the type II collagen triple helical domain [Mortier et al., 1995].

Winterpacht et al. [1993] and later Spranger et al. [1994] described two unrelated patients with KD. In the first patient the disorder was caused by a 28 base exon 12/intron 12 deletion in the gene coding for type II collagen. Her mother had mild abnormalities of the vertebral bodies and long bones compatible with abnormalities seen in Stickler arthro-ophthalmopathy. The second child had a transition of AG to GG at the 3′ splice site of intron 20 of the COL2A1 gene. Her father had a premature polyarthrosis interpreted as a sequela of mild spondyoepiphyseal dysplasia. Molecular studies demonstrated that the mother of the first and the father of the second child each had somatic mosaicism of the same mutation as their children. They concluded that heterozygous mutations of the gene coding for type II collagen can cause KD, and somatic mosaicism for the same mutations can result in the Stickler phenotype or in mild spondyloepiphyseal dysplasia leading to premature polyarthrosis.

Wilkin et al. [1994] have found that a single amino acid substitution (G103D) in the type II collagen triple helix results in KD. These data demonstrate that point mutations which result in single amino acid substitutions can produce KD and further support the hypothesis that alteration of a domain, which includes the region encoded by exon 12, in the type II collagen protein leads to this disorder [Wilkin et al., 1994].

Electron micrographs of cartilage have shown intracellular inclusion bodies, which were stained by an an-

tibody to alpha 1(TT) procollagen. These findings support the hypothesis that alpha-chain length alterations that preserve the Gly-X-V repeat motif of the triple helix result in partial intracellular retention of alpha 1(TT) procollagen and produce mild to moderate chondrodysplasia phenotypes [Tiller et al., 1995].

Using gel-electrophoresis screening for link proteins, cartilage oligomeric matrix protein (COMP) and fibromodulin were found to be normal in KD [Stanescu et al., 1994]. The main band of fibromodulin had a normal migration rate in fibrochondrogenesis, Desbuquois dysplasia, KD, and pseudoachondroplasia. It was delayed in diastrophic dysplasia [Stanescu et al., 1994].

Ocular manifestations of KD have included abnormal long axial length causing high myopia, and vitreoretinal degeneration, cortical and posterior subcapsular opacity of the lens, veil-like vitreous opacity in the periphery, and congenital glaucoma [Kagotani et al., 1995; Mawn et al., 1990].

Dyssegmental dysplasia is an autosomal recessive lethal chondrodysplasia with clinical similarity to KD [Greco et al., 1984; Gruhun et al., 1978]. A short turnk, short neck, and campomelia characterize the condition. Radiologically the appendicular bones show large metaphyses, as in KD, but there is a more pronounced bending of the diaphyses. As mentioned in the section on radiology, the vertebral bodies and the pelvic bones are similar but not identical to KD. In 1987, Aleck et al. demonstrated at least two distinct forms. The milder form, type Rolland-Desbuquois, is characterized by frequent survival beyond the newborn period and by radiological resemblance to KD. The severe form, type Silverman-Handmaker, is characterized by perinatal death and by more severe radiographic changes.

Histopathological examination of the cartilage in the Silverman-Handmaker type demonstrates characteristic puddle-like spaces filled with mucoid material in the resting cartilage [Aleck et al., 1987; Greco et al., 1984; Gruhn et al., 1978]. The physeal growth zone may be retarded. There are large unfused calcospherites in the growth plate and calcifying zones. In the Rolland-Desbuquois type, the resting cartilage has extensive prominent patches of broad collagen fibers and the growth plate is relatively normal. The resting cartilage with myxoid changes, cystic formation, sparse collagen fibrils, and PAS positive inclusions are similar; however, the growth plate is somewhat disorganized in KD but is relatively normal in dyssegmental dysplasia.

As discussed in the section on radiological findings in the newborn, KD has a characteristic combination of changes in the long tubular bones, the pelvis, and the vertebrae at this age. Confusion most often occurs when the position of the pelvis results in an atypical appearance of the ilia. If abnormalities in the limbs and spine suggest KD, re-examination of the pelvis with an effort to avoid forward or backward tilt or rotation should clarify the diagnosis. The diagnosis of KD is always possible sometime in early childhood because of a characteristic evolution of the bony changes. Usually appearing between age 12 and 24 months there is a finding that is diagnostic of KD when it occurs at this age. This consists of irregularity of the distal surface of one or more proximal phalanges with a pseudoepiphysis or small bony centers immediately adjacent [Spranger et al., 1974]. The finding of mild Kniest-like changes on radiological examination should raise the possibility of somatic mosaicism as demonstrated by the Mainz group [Winterpacht et al., 1993; Spranger et al., 1994].

Prenatal diagnosis of KD by ultrasonography has been made [Bromley, 1991; Kerleroux et al., 1994].

REFERENCES

Aleck KA, Grix A, Clericuzio C, Kaplan P, Adomian GE, Lachman R, Rimoin DL (1987): Dyssegmental dysplasia: Clinical, radiographic, and morphologic evidence of heterogeneity. Am J Med Genet 27: 295–312.

Brill PW, Kim HJ, Beratis NG, Hirschhorn K (1975): Skeletal abnormalities in the Kniest syndrome with mucopolysacchariduria. Am J Roentgenol 125:731–738.

Bromley R, Miller W, Foster SC, Benacerraf BR (1991): The prenatal sonographic features of Kniest syndrome. J Ultrasound Med 10: 702–707.

Chen H, Yang SS, Gonzalez E (1980): Kniest dysplasia: Neonatal death with necropsy. Am J Med Genet 6:171–178.

Dinno ND, Shearer L, Weisskopf B (1976): Chondrodysplastic dwarfism, cleft palate and micrognathia in a neonate, a new syndrome? Eur J Pediatr 123:39–42.

Giedion A, Brandner M, Lecannellier J, Muhar U, Prader A, Sulzer J, Zweymüller E (1982): Oto-spondylo-megaepiphyseal dysplasia (OSMED). Helv Pediatr Acta 37:361–380.

Gilbert EF, Yang SS, Langer L, Opitz JM, Roskamp JO, Heidelberger KP (1987): Pathologic changes of osteochondrodysplasia in infancy. In Sommers S (ed): "Pathology Annual." New York: Appleton-Century-Crofts, pp 281–345.

Greco MA, Alvarez SP, Genieser NB, Becker MH (1984): Dyssegmental dwarfism: a histologic study of osseous and nonosseous cartilage. Hum Pathol 15:490–493.

Gruhn JG, Gorlin RJ, Langer LO Jr (1978): dyssegmental dwarfism: A lethal anisospondylic camptomicromelic dwarfism. Am J Dis Child 132:382–386.

Horton WA, Rimoin DL (1979): Kniest Dysplasia: A histochemical study of the growth plate. Pediatr Res 13:1266–1270.

Insley J, Astley R (1974): A bone dysplasia with deafnewss. Br J Radiol 47:244–251.

Kagotani V, Takao K, Nomura K, Okubo K (1995): Two cases of Kniest dysplasia: Ocular manifestations. Nippon Ganka Gakkai Zasshi 99:376–383.

Kelly TE, Wells HH, Tuck KB (1982): The Weissenbacher-Zweymuller syndrome. Am J Med Genet 11:113–119.

Kerleroux J, Roux MS, Cottin X (1994): The difficulty of prenatal diagnosis of Kniest's disease. Apropos of a case simulating congenital spondylo-epiphyseal dysplasia. J Gynecol Obstet Biol Reprod (Paris) 23:69–74.

Kim HJ, Beratis NG, Brill P, Raab E, Hirschhorn K, Matalon R (1975): Kniest syndrome with dominant inheritance and mucopolysacchariduria. Am J Hum Genet 27:755–764.

Lachman RS, Rimoin DL, Hollister DW, Dorst JP, Siggers DC, McAlister W, Kaufman RL, Langer LO Jr (1975): The Kniest syndrome. Am J Roentgenol 123:805–814.

Langer LO Jr: Personal communication, 1980.

Langer LO Jr, Gonzalez-Ramos M, Chen H, Espiritu CE, Courtney NW, Opitz JM (1976): A severe infantile micromelic chondrodysplasia which resembles Kniest disease. Eur J Pediatr 123:29–38.

Larose JH, Gay BB Jr (1969): Metatropic dwarfism (Case 1). Am J Roentgenol 106:156–161.

Maroteaux P, Spranger J (1973): La maladie de Kniest. Arch Fr Pediat 30:735–750.

Mawn LA, O'Brien JE, Hedges RD 3d (1990): Congenital glaucoma and skeletal dysplasia. J Pediatr Ophthalmol Strabismus 27: 322–324.

Mortier GR, Wilkin DJ, Wilcox WR, Rimoin DL, Lachman RS, Ryre DR, Cohn DH (1995): A radiographic, morphologic, biochemical and molecular analysis of a case of achondrogenesis type II result-

ing from substitution for a glycine residue (Gly691→Arg) in the type II collagen trimer. Hum Mol Genet 4:285–288.

Rimoin DL (1975): The chondrodystrophies. Adv Hum Genet 5:1–118.

Rimoin DL, Hollister DW, Lachman RS, Kaufman RL, McAlister WH, Rosenthal RE, Hughes GNF (1974): Histologic studies in the chondrodystrophies. In Bergsma D (ed): "Skeletal Dysplasia." New York: Alan R. Liss for the National Foundation—March of Dimes. BD: OAS X(12):274–295.

Rimoin DL, Hollister DW, Siggers D, Silberberg R, Lachman R, McAlister W, Kaufman R, McKusick VA, Dorst J (1979): Clinical, radiographic, histologic, and ultrastructural definition of the Kniest syndrome. Pediatr Res 13:1266–1270.

Rimoin DL, Silberberg R, Hollister DW (1976): Chondro-osseous pathology in the chondrodystrophies. Clin Orthop 114:137–152.

Roaf R, Longmore JB, Forrester RM (1967): A childhood syndrome of bone dysplasia, retinal detachment, and deafness. Dev Med Child Neurol 9:464–473.

Rolland J-C, Laugier J, Grenier B, Desbuquois G (1972): Nanisme chondrodystrophique et division palatine chez un nouveau-né. Ann Pédiatr (Paris) 19:239–243.

Siggers DC, Rimoin DL, Dorst JP, Doty SB, Williams BR, Hollister DW, Silberberg R, Cranley RE, Kaufman RL, McKusick VA (1974): The Kniest syndrome. In Bergsma D (ed): "Skeletal Dysplasia." New York: Alan R. Liss for the National Foundation—March of Dimes. BD:OAS X(9):193–208.

Silberberg R (1974): Ultrastructure of cartilage in chondodystrophies. In Bergsmas D (ed): "Skeletal Dysplasia." New York: Alan R. Liss for the National Foundation—March of Dimes. BD:OAS X(12): 306–313.

Silverman FN (1969): Discussion (Cincinnati case, Figs. 1–5). In Bergsma D (ed): "Skeletal Dysplasia." New York: Alan R. Liss for the National Foundation—March of Dimes. BD:OAS V(4):45–47.

Spranger JW, Langer LO, Wiedemann H-R (1974): "Bone Dysplasias: An Atlas of Constitutional Disorders of Skeletal Development." Philadelphia, Toronto: WB Saunders Co., pp 95–101 (spondyloepiphyseal dysplasia congenita), pp 114–1192 (Kniest dysplasia).

Spranger JW, Maroteaux P (1974): Kniest disease. In Bergsma D (ed): "Skeletal Dysplasia." New York: Alan R. Liss for the National Foundation—March of Dimes. BD:OAS X(12):50–56.

Spranger J, Menger H, Mundlos S, Winterpacht A, Zabel R (1994): Kniest dysplasia is caused by dominant collagen TT (COL2A1) mutations: Parental somatic mosaicism manifesting as Stickler phenotype and mild spondyloepiphyseal dysplasia. Pediatr Radiol 24:431–435.

Spranger J, Winterpacht, Zabel R (1994): The type II collagenopathies: A spectrum of chondrodysplasias. Eur J Pediatr 153: 56–65.

Stanescu V, Do TP, Chaminade F, Maroteaux P, Stanescu R (1994): Non-collagenous preotein screening in the human chondrodysplasias: Link proteins, cartilage oligomeric matrix protein (COMP), and fibromodulin. Am J Med Genet 51:22–28.

Stanescu V, Maroteaux P (1975): Gel electrophoretic studies on proteoglycans and collagen of abnormal human growth cartilage: Proteoglycan abnormalities in pseudoachondroplasia and in Kniest's disease. Pediatr Res 9:779–782.

Stanescu V, Stanescu R, Maroteaux P (1977): Etude morphologique et biochimique du cartilage de croissance dans les osteochondrodysplases. Arch Franç Pediatr 34:48.

Taybi H, Lachman R (1990): "Radiology of Syndromes, Metabolic Disorders, and Skeletal Dysplasias." Chicago, London: Yeark-Book Medical Publishers, Inc., pp 774, 775, 813.

Tiller GR, Weis MA, Polumbo PA, Gruber HR, Rimoin DL, Cohn DH, Ryre DR (1995): An RNA-splicing mutation (G+5TVS20) in the type II collagen gene (COL2A1) in a family with spondyloepiphyseal dysplasia congenita. Am J Hum Genet 56:388–395.

Wilkin DJ, Rogaert R, Lachman RS, Rimoin DL, Ryre DR, Cohn DH (1994): A single amino acid substitution (G103D) in the type II collagen triple helix produces Kniest dysplasia. Hum Mol Genet 3:1999–2003.

Winterpacht A, Hilbert M, Schwarze U, Mundlos S, Spranger J, Zabel RU (1993): Kniest and Stickler dysplasia phenotypes caused by collagen type II gene (COL2A1) defect. Nat Genet 3:323–326.